EDITORIAL

Cardio-Rheumatology: Two Collaborating Disciplines to Deal with the Enhanced Cardiovascular Risk in Autoimmune Rheumatic Diseases

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Abstract: In Part 1 of this Thematic Issue entitled “Systemic Autoimmune Rheumatic Diseases and Cardiology”, a panel of specialists and experts in cardiology, rheumatology, immunology and related fields discussed the cardiovascular complications of spondyloarthritides, rheumatoid arthritis, Sjogren’s syndrome and vasculitides, as well as relevant cardiovascular issues related to non-biologic and biologic disease-modifying anti-rheumatic drugs (DMARDs), and provided their recommendations for prevention and management of these complications. In part 2 of this Thematic Issue, experts discuss the enhanced cardiovascular risk conferred by additional autoimmune rheumatic diseases (ARDs), including systemic lupus erythematosus, the antiphospholipid syndrome, psoriasis and psoriatic arthritis and juvenile idiopathic arthritis. These, and the previous articles, place inflammation as the key common link to explain the enhanced risk of cardiovascular complications in patients with ARDs. It follows that treatment should probably target inflammation. From all these contemporary reviews, the conclusion that is derived further supports the notion of the emerging field of Cardio-Rheumatology where physicians and experts from these two disciplines collaborate in risk stratification and optimization of preventive strategies and drug therapies in patients with ARDs.

Keywords: Autoimmune rheumatic disease, cardiovascular disease, cardiorheumatology, systemic lupus erythematosus, psoriasis, psoriatic arthritis, anti-rheumatic drugs, cardiovascular imaging, coronary artery disease, acute coronary syndromes, atherosclerosis, myocardial infarction, stroke, antiphospholipid syndrome, juvenile idiopathic arthritis.

The enhanced risk of cardiovascular (CV) complications encountered in autoimmune rheumatic diseases (ARDs) has been attributed to a systemic inflammatory state that may be responsible for premature or accelerated atherosclerosis, endothelial dysfunction and a prothrombotic state that may lead to acute coronary events. Furthermore, a host of other CV diseases, such as hypertension, cardiomyopathy, cardiac arrhythmias, metabolic syndrome, pancarditis, vasculitis, and stroke may occur in patients with ARDs (Fig. 1) [1-6]. In Part 1 of this Thematic Issue of Current Vascular Pharmacology (CVP), entitled “Systemic Autoimmune Rheumatic Diseases and Cardiology”, a panel of specialists and experts in cardiology, rheumatology, immunology and related fields discussed the CV complications of spondyloarthritides, rheumatoid arthritis, Sjogren’s syndrome and vasculitides, and described the CV issues associated with the use of non-biologic and biologic disease-modifying anti-rheumatic drugs (DMARDs); they also provided their recommendations for prevention and management of these complications [4-9].

In Part 2 of this Thematic Issue, experts discuss the enhanced CV risk conferred by additional ARDs, including spondyloarthropathies, systemic lupus erythematosus (SLE), antiphospholipid syndrome, psoriasis and psoriatic arthritis, and juvenile idiopathic arthritis [10-14]. In this context, experts from the two disciplines, as advocates of the emerging field of Cardio-Rheumatology, provide their insight into the underlying pathogenetic mechanisms of the ARDs that may explain the enhanced CV risk.

The leading cause of death in the majority of ARDs is related to cardio-cerebro-vascular events (myocardial infarction or stroke) [10]. A variety of CV disorders, including, albeit not limited to, coronary artery disease, hypertension, cardiomyopathy, cardiac arrhythmias, pancarditis, vasculitis, stroke, thromboembolism and pulmonary artery hypertension are encountered in ARDs (Fig. 1). Pathophysiological mechanisms and clinical phenotype of CV comorbidities vary greatly among different ARDs, but atherosclerosis, which may often be premature and/or accelerated, seems to be common to all of them. Atherosclerosis could be subclinical and non-invasive imaging techniques may help assess patients with ARDs. For example, ultrasonographic measurement of the carotid intima-media thickness is a useful method to detect subclinical atherosclerosis and better risk stratify patients compared with methods using traditional CV risk scores, as discussed in the review by Atzeni et al. [10]. In this context, it has been suggested that the value of the clinical risk score should be multiplied by 1.5 for patients with ARDs.

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Fig. (1). The schema illustrates the relationship between cardiovascular (CV) disease (CVD) and autoimmune rheumatic diseases (ARDs) (sectors) with the specific CV complications listed in the respective quadrant. The CV effects of disease-modifying antirheumatic drugs (DMARDs) are also shown at the lower panel. AF = atrial fibrillation; AI = aortic insufficiency; Aneur = aneurysm; AVB = atrioventricular block; BBB = bundle branch block; CAD = coronary artery disease; CoP = constrictive pericarditis; CVA = cerebrovascular accident; JIA = juvenile idiopathic arthritis; HCQ = hydroxychloroquine; HF = heart failure; HTN = hypertension; Ili = interleukin inhibitors; MACE = major cardiovascular events; MyoC = myocarditis; MVD = microvascular dysfunction; NBTE = non-bacterial thrombotic endocarditis; PAD = peripheral artery disease; PAH = pulmonary arterial hypertension; PeriC = pericarditis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SpA = spondyloarthritides; SjS = Sjogren syndrome; SLE = systemic lupus erythematosus; SScl = systemic sclerosis; TNFi = tumour necrosis factor inhibitors; Vasc = vasculitides; VHD = valvular heart disease; VSA = vasospastic angina; VT = ventricular tachycardia; VTE = venous thromboembolism. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

to obtain a more accurate CV risk stratification [10, 15]. CV magnetic resonance (CMR) imaging and new echo strain techniques have also been proposed as imaging tools to demonstrate impaired myocardial deformation and vascular function in asymptomatic ARD patients [16, 17]. Importantly, chronic systemic inflammation and the duration of ARD activity seem to play a major role in the prognosis of patients with ARDs. Atherosclerosis is an athero-thrombo-inflammatory disease, and, as such, systemic inflammatory diseases like ARDs could trigger and/or contribute to its development [18, 19]. Markers of endothelial dysfunction [endothelial-activating cytokines such as interleukin (IL)-1β, IL-6 and tumour necrosis factor alpha (TNF-α)] and systemic biomarkers of inflammation (C-reactive protein, erythrocyte sedimentation rate) and cardiac dysfunction (natriuretic peptide, cardiac troponin) have also been suggested as useful predictors of CV risk and mortality in these patients [10]. Conditions that are common in ARDs, such as inflammation, dyslipidaemia and oxidative stress, may all contribute to endothelial dysfunction, a key process for atherosclerosis and other CV diseases.

Traditional CV risk factors (dyslipidaemia, diabetes, hypertension, smoking, metabolic syndrome), which may have a higher prevalence in patients with ARDs, should be assessed and managed, but one should also be aware of the “lipid paradox” phenomenon in patients with ARDs, where low density lipoprotein cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) may be reduced by systemic inflammation. Patients with active ARDs are also at increased risk of developing CV disease, as chronic inflammation increases some atherogenic apolipoprotein B-containing particles, which further increase CV risk [20]. Traditional CV risk factors, noted to be more prevalent in ARDs, contribute to the increased risk observed in ARDs but cannot fully explain the accelerated CV disease; for example in SLE, suggesting an important additional role of the ARD itself, its duration and activity, and of treatment-related factors [11]. Indeed, there is evidence that an ARD may be an independent CV risk factor as suggested by several studies showing a “time dependent dose effect” of ARD on CV risk [13]. Common inflammatory pathways may be the shared link between ARDs and CV diseases [21].

However, ARDs, in addition to promoting atherosclerosis with its attendant CV events (myocardial infarction, stroke), can also affect all cardiac layers (pericardium, myocardium, endocardium and cardiac valves), the conduction system, and peripheral vessels, all leading to several CV manifestations that can increase morbidity and mortality, as detailed in Part 2 of this Thematic Issue [10-14]. In particular, spondyloarthopathies (ankylosing spondylitis, psoriatic arthritis, reactive arthritis, arthritis associated with chronic inflammatory bowel disease) and SLE can lead to conduction disturbances, aortic insufficiency, pancarditis (pericarditis, myocarditis, endocarditis and valvulitis), cardiomyopathy and heart failure [10, 11]. Several ARDs (e.g. SLE, Sjogren’s syndrome) in pregnant women have been associated with congenital heart block, as circulating maternal anti Ro/SSA and anti La/SSB autoantibodies [22] may injure the atrioventricular node of the embryo [23]. Patients with ARDs have an increased prevalence of hypertension (30-70% in rheumatoid arthritis and SLE), with apparent links to immune system activation and inflammation [24, 25].
Poltyarchou et al. review an important systemic autoimmune, multifactorial, thrombophilic disease, the antiphospholipid syndrome (APS), characterized by venous, arterial or microvascular thrombosis, also associated with endothelial dysfunction, that commonly occurs in the absence of any underlying cause (primary APS) or associated with ARDs, such as SLE or rheumatoid arthritis (secondary APS) [12]. CV complications in APS comprise accelerated atherosclerosis, acute coronary syndromes, nonbacterial thrombotic endocarditis, cardiomyopathy, pulmonary hypertension, venous thromboembolism, and intracardiac thrombi. Anticoagulation is the mainstay of treatment to prevent thromboembolic complications, while data about treatment of the primary initiating pathophysiological mechanism of the syndrome remain scarce.

Arsenaki et al. review juvenile idiopathic arthritis (JIA), the most common ARD in the paediatric population, which may predispose to CV disease via an increased inflammatory burden and an unfavourable CV risk profile observed in these patients, along with any adverse CV effects incurred by DMARDs [14]. It should be noted that JIA, especially in its systemic and polyarticular form, can affect all cardiac structures; CV complications account for increased morbidity and mortality in JIA, with pericardial disease reported in up to 30% of these young patients. Surviving adults have a significantly increased risk of metabolic syndrome compared with their counterparts without a history of JIA [26], possibly related to long-term corticosteroid therapy and its associated insulin resistance [27]. Interestingly, an increased incidence of CV risk factors has been noted in the JIA group with family history of CV disease, history of hypertension and/or smoking [28]. Although there is a gap of knowledge in this patient group regarding longitudinal CV risk, controlling the chronic inflammatory state of JIA by current therapies and managing comorbidities seems prudent as it may provide significant long-term benefits [29, 30].

As also stated in our editorial in Part 1, from these reviews it becomes clear that more aggressive primary and secondary prevention of CV disease is needed in patients with ARDs. Although these patients seem to have a higher prevalence of traditional CV risk factors, the greater than 1.5-fold higher risk of CV disease noted in these patient groups, suggests that each ARD itself may be an independent CV risk factor, in the setting of a chronic inflammatory state responsible for much of the excess risk of CV disease and mortality in these patients [10]. Inflammation contributes to atherosclerosis, endothelial dysfunction, plaque vulnerability, and atherothrombotic events; inflammation may cause myocardial disease directly, leading to heart failure (HF), accounting for a >2-fold increase in HF in patients with ARDs and not fully explained by CV risk factors or ischaemic heart disease. As also mentioned, nuclear factor kappa B (NFkB), a major transcription factor, with crucial roles in the regulation of inflammation and immune responses in ARDs, has been linked, via cell-specific effects, to both CV health and disease, including atherosclerosis, myocardial ischaemia and preconditioning, cardiac hypertrophy and HF [31, 32]. The cell-specific effects of NFkB and its influence on disease processes (e.g. NFkB activity in endothelial cells is pro-atherogenic, whereas NFkB activity in macrophages can be anti-atherogenic) [31], suggest that keeping NFkB activation under control can be very important for the design of specific therapeutics for both CV disease and ARD [31, 33].

The message that becomes clear from the reviews included in this Thematic Issue is that there should be a dual target in the management of patients with ARDs including control of CV risk factors, CV disease and ARD activity [5, 7]. At earlier stages of an ARD, aggressive management and control of traditional CV risk factors (hypertension, dyslipidaemia, smoking and diabetes) should be implemented. ARD activity and duration reflecting the inflammatory status and its potential impact on CV diseases, should also constitute key target for prevention of CV disease. Anti-inflammatory therapies with DMARDs may help decrease ARD activity. However, the effects of DMARDs, detailed in Part 1 by Mourouzis et al. and Drakopoulou et al., need to be taken into consideration, as not all of them may mitigate the CV risk but some may enhance CV risk [8, 9]. A cardioprotective effect has been observed with use of the non-biologic DMARDs, methotrexate and hydroxychloroquine, and the biologic DMARDs, TNF inhibitors, but other agents, such as corticosteroids, non-steroidal anti-inflammatory drugs and interleukin inhibitors, may adversely affect CV diseases. Furthermore, even for TNF inhibitors, there is concern for patients with symptomatic or asymptomatic left ventricular dysfunction, where these agents may induce or exacerbate congestive heart failure symptoms and are thus contraindicated in these patients [8, 9]. Hence, careful selection of these treatments is of paramount importance. Also, more data will be needed to further guide an optimal approach and strategy [7].

The information detailed in all the reviews included in this Thematic Issue, support a role for a “Cardio-Rheumatology” subspecialty. This reinforces our conviction that collaboration between Rheumatology and Cardiology will help refine risk stratification and optimize treatment in patients with ARDs [34].

LIST OF ABBREVIATIONS

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<th>Abbreviation</th>
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<tr>
<td>APS</td>
<td>Antiphospholipid Syndrome</td>
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<td>ARDs</td>
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<td>CMR</td>
<td>Cardiac Magnetic Resonance</td>
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<td>HDL-C</td>
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<td>IL</td>
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REFERENCES


http://dx.doi.org/10.2147/OARRR.S157229 PMID: 29922101

http://dx.doi.org/10.1186/s12969-018-0302-5 PMID: 30594204

http://dx.doi.org/10.3109/03009742.2015.1126345 PMID: 26854592

http://dx.doi.org/10.1007/s00296-016-3534-z PMID: 27417551

PMID: 23557722

http://dx.doi.org/10.1042/CS20090557 PMID: 20175746

http://dx.doi.org/10.1186/ar3324 PMID: 21639951

http://dx.doi.org/10.1186/ar2157 PMID: 18771589

http://dx.doi.org/10.1038/nrcardio.2014.206 PMID: 25533796